PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial)
AUTHORS	Chan, Vincent; Chu, Michael; Leong-Poi, Howard; Latter, David; Hall, Judith; Thorpe, Kevin; de Varennes, Benoit; Quan, Adrian; Tsang, Wendy; Dhingra, Natasha; Yared, Kibar; Teoh, Hwee; Chu, F Victor; Chan, Kwan-Leung; Mesana, Theirry; Connelly, Kim; Ruel, Marc; Jüni, Peter; Mazer, David; Verma, Subodh

VERSION 1 - REVIEW

REVIEWER	Gerald M Lawrie Houston Methodist Hospital Texas USA
REVIEW RETURNED	14-Nov-2016

GENERAL COMMENTS	ETHICS. Have the authors confirmed by submission of data that all surgeons in the study are equally proficient and experienced with both surgical techniques. STUDY DESIGN This is a concern. It is a multicenter study. Therefore data collection must be standardized by use of pre planned data collection protocols. A major problem with analysis of mitral valve surgery results is introduction of selection biases arising from excluding patients from study enrollment. These may include perceived risk of potential repair complexity or anticipation of need for replacement as exclusion criteria preoperatively. Thus all patients who undergo mitral surgery during the study period who meet the the valve pathology criteria for inclusion described must be recorded whether they were enrolled, excluded or had replacement.. Then the reasons for non-inclusion in the study must be documented. Otherwise in some centers patients treated by surgeons who feel they could repair the valve by one technique but not another would be unable to be analyzed accurately. The true repair rate of each surgeon and each technique could then be documented. Similarly if the 2 techniques of repair are considered comparable and all the surgeons in the study are equally adept at both types of repair, then the enrollment must surely be made on the basis of the pre-operative echo, not intraoperatively. The details of the valve pathology must be recorded in detail as this may introduce biases. For example, if all patients had small p2 prolapses and could be treated by small triangular resections, a point would be reached at which functionally the valve could resemble a non resected valve. On the other hand, if the posterior leaflet had extensive multisegment leaflet prolapse, the surgeon may decide that chordae are a better option in most cases. If intraoperative randomization is used, many surgeons may exclude this type of patient completely because it may clearly be a valve which after extensive resection would be prone to be stenotic. This would introduce a bias favorable to resection because of exclusion

	of suboptimal cases for resection. ECHOCARDIOGRAPHY The absence of 3D echo or annular tracking may reduce the reliability of the data regarding pre and post-op annular dimensions at rest. This data could be obtained intraoperatively and would be of value . SURGICAL TECHNIQUE There is a large volume of data available now regarding the importance of preservation of mitral annular dynamics in mitral valve repair. Miller et al have documented that the D shaped semi rigid Physio ring acts like a rigid ring.There needs to be a more detailed discussion as to why this ring was chosen when it by itself can produce mitral stenosis and SAM regardless of the leaflet repair technique. As discussed in our recent paper these rings reduce annular and LVOT dimensions. In this paper resting mitral gradients predischarge were1.8+/-2.2mm. The paper contains no discussion of the important role of the annulus in avoiding MS and SAM. The authors also need to consider the documented role of semi rigid rings in the production of LVOT gradients and SAM. This data should also be collected.This aspect of the study and discussion of the literature should be expanded. The reviewer also provided a file in addition to these comments. Please contact the publisher for full details.

REVIEWER	Dr Liam Ring West Suffolk Hospital NHS Foundation Trust
REVIEW RETURNED	30-Nov-2016

GENERAL COMMENTS	Overall I think that the underlying principle of the study is interesting and sets about answering an important question. The study methods are well described. I have a few concerns. 1. The authors use Reference 18 as a rationale for their study: in particular they mention that the previous work demonstrated that use of leaflet preservation may be associated with less functional mitral stenosis. The authors cannot use this reference to support that theory: in the earlier work, there is relatively little difference in the surgical techniques between the two groups (other than more plication in the group with functional MS) IN fact use of resection was identical between the two groups. The main difference between the groups was the use of a complete annular ring and the conclusion mentions this as an important potential cause of functional MS (which is why annular rings are being standardised in the proposed study). The authors should therefore re-phrase the document (Page 11, Lines 25 onward) to better reflect that earlier work. 2. It has been highlighted by the authors' that there are some limitations: in particular, owing to the relatively short follow up the long-term robustness of surgical strategy cannot be determined. The decision as to the particular type of mitral repair techniques will be made only after the surgeon has determined that both techniques are feasible. In my experience, surgeons frequently have a preferred method of repair (i.e. will usually pursue a leaflet preservation OR a leaflet resection strategy). Are the surgeons involved in the trial equally practised at each method? If not, the study might simply represent an individual surgeons skill of one technique over another.

	3. In 'Ethics and Dissemination' (Page 11, line 30) the authors state that '110 patients who underwent repair of MR due to myxomatous degeneration were divided into those that had a mean intraoperative mitral gradient ≤3 mm Hg and >3 mm Hg'. On reading the original manuscript to which that refers, I got the impression that the included patient were divided according to the mean mitral valve gradient at the time of post operative echocardiography NOT the intra-operative gradient. Could this be clarified please. Although I appreciate that I am asking questions regarding a prior manuscript, it would appear to have a direct implication on the central rationale for this particular study. 4. In addition, it is not proposed that pre-repair haemodynamic data is recorded. I am not a statistician, but my understanding is that as the included patients will be randomised to one of the two groups, differences in baseline characteristics between the two study groups may occur but will not invalidate the results. However, as the randomisation is based upon surgical opinion as to each patient being suitable for both techniques I am not sure whether this could potentially influence the inclusion or results: I would value a statistician's opinion on this and I wonder whether pre-operative mean MV gradient along with other data should potentially be included in the multivariate model. 5. The assessment of mitral orifice area will be obtained using planimetry in the parasternal short axis window. Although this is an acceptable method, it is highly dependent both on operator skill and window quality. I am concerned that as an isolated method it is perhaps not reliable enough to demonstrate a consistent difference between direct study groups. This would particularly be the case for individuals in AF: can the authors state what they would do in this situation? I would possibly advocate the use of 3D echo for planimetry, which certainly improves accuracy, or an additional method of mitral area calculation, for example the continuity method. 6. I am not sure why mitral leaflet coaptation height is a secondary endpoint: it bears no relationship to the primary stated aim of the study, and does not appear to be associated with the concern regarding functional MS.

REVIEWER	Alfonso Muriel Unidad de Bioestadística Clínica Hospital Ramón y Cajal. IRYCIS CIBERESP Madrid Spain
REVIEW RETURNED	20-Dec-2016

GENERAL COMMENTS	Authors should specify how the missing data (death, dropout of the study) are imputed to the primary endpoint. If MACE is analyzed by Kaplan Meier univariate, Cox regression should be used to adjust for other confounders, no logistic regression. The statistical analysis should contemplate if the contrasts are bilateral, the statistical package, significance level.

VERSION 1 – AUTHOR RESPONSE

Comments by Reviewer #1
Comment #1: ETHICS. Have the authors confirmed by submission of data that all surgeons in the study are equally proficient and experienced with both surgical techniques.
Response: This study involves surgeons and centres familiar with mitral valve reconstruction, thereby minimizing the risk to the patient. Although individual surgeon data was not required by each institutional ethics review board, patients will be subjected to several postoperative echocardiographic assessments, which goes beyond the structure of follow-up typically performed at most operating centres. Therefore, the harm to individual patients is thought not to be great.

Comment #2: STUDY DESIGN This is a concern. It is a multicenter study. Therefore data collection must be standardized by use of pre planned data collection protocols. A major problem with analysis of mitral valve surgery results is introduction of selection biases arising from excluding patients from study enrollment. These may include perceived risk of potential repair complexity or anticipation of need for replacement as exclusion criteria preoperatively. Thus all patients who undergo mitral surgery during the study period who meet the valve pathology criteria for inclusion described must be recorded whether they were enrolled, excluded or had replacement. Then the reasons for non-inclusion in the study must be documented. Otherwise in some centers patients treated by surgeons who feel they could repair the valve by one technique but not another would be unable to be analyzed accurately. The true repair rate of each surgeon and each technique could then be documented. Similarly if the 2 techniques of repair are considered comparable and all the surgeons in the study are equally adept at both types of repair, then the enrollment must surely be made on the basis of the pre-operative echo, not intraoperatively. The details of the valve pathology must be recorded in detail as this may introduce biases. For example, if all patients had small p2 prolapses and could be treated by small triangular resections, a point would be reached at which functionally the valve could resemble a non resected valve. On the other hand, if the posterior leaflet had extensive multisegment leaflet prolapse, the surgeon may decide that chordae are a better option in most cases. If intraoperative randomization is used, many surgeons may exclude this type of patient completely because it may clearly be a valve which after extensive resection would be prone to be stenotic. This would introduce a bias favorable to resection because of exclusion of suboptimal cases for resection.
Response and revisions: This Reviewer raises an important concern regarding the external validity of randomized trials [1]. He is entirely correct that enrolled patients may not be reflective of the entire population of patients undergoing mitral repair. In fact, we have previously shown that patients initially reported to have isolated prolapse of the middle scallop of the posterior leaflet had complex prolapse involving other scallops when analyzed intraoperatively [2]. In order to adequately frame the external validity of the study, the number of patients with prolapse treated at each enrolling center during the study period will be included in the final report of the study results. Please see attached revision on page 10 of the revised, marked manuscript.
It is important to note that the objective of this trial is to compare the hemodynamic consequences of either a leaflet resection or a leaflet preservation approach. Randomization of patients after the surgeon has deemed that either valve repair technique minimizes technique cross-over, which could confound the study results. Although the repair rate of each surgeon is important, it is not the primary study objective. Recurrent mitral regurgitation following repair will be reported as this can impact valve hemodynamics following repair.
References
1. Rothwell P. Factors That Can Affect the External Validity of Randomised Controlled Trials. 2. PLoS Clin Trials. 2006 May; 1(1): e9.
2. Grisoli D, Chan V, Tran A, Ressler L, Nicholson D, Hynes M, Ruel M, Mesana TG. Frequency and surgical management of complex posterior leaflet prolapse of the mitral valve. J Heart Valve Dis. 2010 Sep;19(5):568-75.

Comment #3: ECHOCARDIOGRAPHY The absence of 3D echo or annular tracking may reduce the

reliability of the data regarding pre and post-op annular dimensions at rest. This data could be obtained intraoperatively and would be of value."
Response: Three-dimensional transesophageal echocardiography was not mandated in this trial since it is not readily accessible to all patients undergoing cardiac surgery. Nevertheless, a thorough TEE assessment will be performed for all patients. Importantly, the conventional anterior-posterior and commissure-commissure obtained via 2D echocardiography has been shown to yield accurate mitral annulus area measurements compared to 3D planimetric methods [1].
Reference
1. Hyodo E, Iwata S, Tugcu A et al, Accurate measurement of mitral annular area by using single and biplane linear measurements: comparisonof conventional methods with the three-dimensional planimetric method. Eur Heart J Cardiovasc Imaging. 2012 Jul;13(7):605-11. doi: 10.1093/ejechocard/jer300. Epub 2011 Dec 30.

Comment #4: SURGICAL TECHNIQUE There is a large volume of data available now regarding the importance of preservation of mitral annular dynamics in mitral valve repair. Miller et al have documented that the D shaped semi rigid Physio ring acts like a rigid ring.There needs to be a more detailed discussion as to why this ring was chosen when it by itself can produce mitral stenosis and SAM regardless of the leaflet repair technique. As discussed in our recent paper these rings reduce annular and LVOT dimensions. In this paper resting mitral gradients predischarge were1.8+/-2.2mm. The paper contains no discussion of the important role of the annulus in avoiding MS and SAM. The authors also need to consider the documented role of semi rigid rings in the production of LVOT gradients and SAM. This data should also be collected.This aspect of the study and discussion of the literature should be expanded.
Response and revisions: The Reviewer raises an important point. The Physio ring was selected since this represents a commonly used annuloplasty ring system in the surgical treatment of mitral regurgitation [1-2]. Overall, favorable early and late results have been described following mitral repair employing the Physio II ring [1-2].
References
1. Vohra HA, Whistance RN, Bezuska L, Livesey SA. Initial experience of mitral valve repair using the Carpentier-Edwards Physio II Annuloplasty ring. Eur J Cardiothorac Surg. 2011 Jun;39(6):881-5. doi: 10.1016/j.ejcts.2010.10.004. Epub 2010 Nov 23.
2. Castillo JG, Anyanwu AC, Fuster V, et al. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. J Thorac Cardiovasc Surg 2012;144:308-12. doi: 10.1016/j.jtcvs.2011.12.054

Comments by Reviewer #2
Comment #1: "The authors use Reference 18 as a rationale for their study: in particular they mention that the previous work demonstrated that use of leaflet preservation may be associated with less functional mitral stenosis. The authors cannot use this reference to support that theory: in the earlier work, there is relatively little difference in the surgical techniques between the two groups (other than more plication in the group with functional MS) IN fact use of resection was identical between the two groups. The main difference between the groups was the use of a complete annular ring and the conclusion mentions this as an important potential cause of functional MS (which is why annular rings are being standardised in the proposed study). The authors should therefore re-phrase the document (Page 11, Lines 25 onward) to better reflect that earlier work."
Response and revision: Thank you for this important comment. In previous work performed by Chan K et al., 110 patients who underwent repair of MR due to myxomatous degeneration were divided into those that had a mean intraoperative mitral gradient ≤3 mm Hg and >3 mm Hg. Patients with a higher mean trans-mitral repair gradient were more likely to undergo leaflet resection with annular plication. This information has been added to page 12 of the revised, marked manuscript.

Comment #2: It has been highlighted by the authors' that there are some limitations: in particular,

owing to the relatively short follow up the long-term robustness of surgical strategy cannot be determined. The decision as to the particular type of mitral repair techniques will be made only after the surgeon has determined that both techniques are feasible. In my experience, surgeons frequently have a preferred method of repair (i.e. will usually pursue a leaflet preservation OR a leaflet resection strategy). Are the surgeons involved in the trial equally practised at each method? If not, the study might simply represent an individual surgeons skill of one technique over another.
Response and revision: The Reviewer is entirely correct that surgical comfort with either repair technique is required to mitigate study cross-over. This study involves surgeons and centres familiar with mitral valve reconstruction, thereby minimizing the risk to the patient. We have previously reported our repair outcomes in treating patients with degenerative disease due to bileaflet prolapse [1].

Reference
1. Chan V, Ruel M, Chaudry S, Lambert S, Mesana T. Clinical and echocardiographic outcomes after repair of mitral valve bileaflet prolapse due to myxomatous disease. J Thorac Cardiovasc Surg 2012; Apr: 143(4 Suppl):S8-11.

Comment #3: 'In 'Ethics and Dissemination' (Page 11, line 30) the authors state that '110 patients who underwent repair of MR due to myxomatous degeneration were divided into those that had a mean intraoperative mitral gradient ≤3 mm Hg and >3 mm Hg'. On reading the original manuscript to which that refers, I got the impression that the included patient were divided according to the mean mitral valve gradient at the time of post operative echocardiography NOT the intra-operative gradient. Could this be clarified please. Although I appreciate that I am asking questions regarding a prior manuscript, it would appear to have a direct implication on the central rationale for this particular study."
Response: The author is correct that our preliminary data involved assessments of intraoperative trans-mitral gradients.

Comment #4: "In addition, it is not proposed that pre-repair haemodynamic data is recorded. I am not a statistician, but my understanding is that as the included patients will be randomised to one of the two groups, differences in baseline characteristics between the two study groups may occur but will not invalidate the results. However, as the randomisation is based upon surgical opinion as to each patient being suitable for both techniques I am not sure whether this could potentially influence the inclusion or results: I would value a statistician's opinion on this and I wonder whether pre-operative mean MV gradient along with other data should potentially be included in the multivariate model."
Response and revision: The Reviewer raises a concern that patient groups may not necessarily be balanced even after study randomization. Although this is not thought to be likely, baseline characteristics will be compared between groups using a chi-square test for categorical variables or a Student's t-test for continuous variables. This information has been added to page 10 of the revised, marked manuscript.

Comment #5: "The assessment of mitral orifice area will be obtained using planimetry in the parasternal short axis window. Although this is an acceptable method, it is highly dependent both on operator skill and window quality. I am concerned that as an isolated method it is perhaps not reliable enough to demonstrate a consistent difference between direct study groups. This would particularly be the case for individuals in AF: can the authors state what they would do in this situation? I would possibly advocate the use of 3D echo for planimetry, which certainly improves accuracy, or an additional method of mitral area calculation, for example the continuity method."
Response and revisions: The Reviewer raises an important concern. Three-dimensional echocardiography is not mandated in this study since it is not readily available at all enrolling centers. However, verifying mitral valve area with the continuity method is easily performed and, therefore, we have included this into our study protocol. This information has been added to page 8-9 of the revised, marked manuscript.

Comment #6: “I am not sure why mitral leaflet coaptation height is a secondary endpoint: it bears no relationship to the primary stated aim of the study, and does not appear to be associated with the concern regarding functional MS.”
Response: Mitral leaflet coaptation height will be assessed since it has been speculated to be better following repair of degenerative mitral regurgitation employing a leaflet preservation (neochordae) approach.

References:
1. Falk V, Seeburger J, Czesla M, et al. How does the use of polytetrafluoroethylene neochordae for posterior mitral valve prolapse (loop technique) compare with leaflet resection? A prospective randomized trial. J Thorac Cardiovasc Surg 2008;136:1205; discussion 05-6. doi: 10.1016/j.jtcvs.2008.07.028
2. Seeburger J, Falk V, Borger MA, et al. Chordae replacement versus resection for repair of isolated posterior mitral leaflet prolapse: a egalite. Ann Thorac Surg 2009;87:1715-20. doi: 10.1016/j.athoracsur.2009.03.003

Comments by Reviewer #2

Comment #1: “Authors should specify how the missing data (death, dropout of the study) are imputed to the primary endpoint.”
Response: Missing data for the primary outcome is unlikely to be missing at random and so standard imputation approaches are problematic. Therefore two analyses will be conducted if the primary outcome is missing in more than 5% of the subjects. The first will be the usual complete case analysis. The second will employ inverse probability weighting on the probability of "completing" the study. If these analyses are concordant, the simpler analysis will be primary.

Comment #2: “If MACE is analyzed by Kaplan Meier univariate, Cox regression should be used to adjust for other confounders, no logistic regression.”
Response and revisions: The proportion of individuals experiencing the composite major adverse cardiac end-point of recurrent MR ≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery will be compared between groups using method chi-square test. Risk factors associated with the composite end-point will also be assessed by logistic regression in order to determine the adjusted impact of the mitral repair strategy on outcomes. These changes have been made on page 10 of the revised, marked manuscript.

Comment #3: “The statistical analysis should contemplate if the contrasts are bilateral, the statistical package, significance level.”
Response and revisions: A two-sided significance level of 5% will be used throughout. This change has been made on page 10 of the revised, marked manuscript.

VERSION 2 – REVIEW

REVIEWER	Dr Liam Ring West Suffolk Hospital NHS Foundation Trust England
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	I think they have addressed my concerns